



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

(MBHB00,882-C, 400.019)

In the Application of:

Chowrira, et al.

Serial No. 09/653,225

Filed: August 31, 2000

For: METHOD AND REAGENT FOR THE
INHIBITION OF TELOMERASE ENZYME

Before the Examiner:

Group Art Unit: 1651

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

TRANSMITTAL LETTER

In regard to the above identified application:

1. We are transmitting herewith the attached papers for the above identified new patent application:

- Information Disclosure Statement;
- Information Disclosure Statement (IDS) PTO-1449 Form;
- Copies of IDS Citations for S/N 09/653,225 (Total 3 U.S. Patent Application Documents, 15 patents, 27 foreign patents and 138 other documents); and
- Return Receipt Postcard.

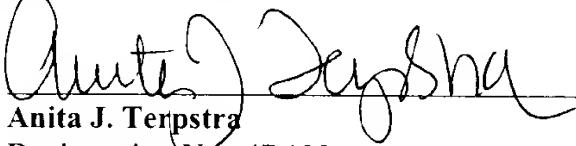
2. With respect to additional fees:

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By:


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INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Pursuant to the duty of disclosure provided by 37 C.F.R. §1.56 and §§1.97-98, the applicants wish to make the following references of record in the above-identified application. Copies of the references are enclosed. Copies are also listed in the PTO-1449 form enclosed herewith. It is requested that each document cited (including any cited in applicant's specification which is not repeated on the attached Form PTO-1449) be given thorough consideration and that it be cited of record in the prosecution history of the present application by initialing on Form PTO-1449. Such initialing is requested even if the Examiner does not consider a cited document to be sufficiently pertinent to use in a rejection, or otherwise does not consider it to be prior art for any reason, or even if the Examiner does not believe that the guidelines for citation have been fully complied with. This is requested so that each document becomes listed on the face of the patent issuing on the present application.

Portions of the references may be material to the examination of the pending claims, however no such admission is intended. 37 C.F.R. §1.97 (h). The references have not been reviewed in sufficient detail to make any other representation and, in particular, no representation is intended as to the relative importance of any portion of the references. This Statement is not a representation that the cited references have effective dates early enough to be "prior art" within the meaning of 35 U.S.C. §§ 102 or 103.

CITED REFERENCES

U.S. Patent Application Documents

	Document Number	Filing Date	Name
1	09 301,511	04/28/99	Beigelman, et al.
2	60 082,404	04/20/98	Thompson, et al.
3	60 101,174	9/21/98	Hartmann et al.

U.S. Patent Documents

	Document Number	Date	Name
4	4 987,071	01/22/91	Cech et al.
5	5 334 711	08/02/94	Sproat et al.
6	5 359 051	10/25/94	Cook et al.
7	5 489 508	02/06/96	West et al.
8	5 525 468	06/11/96	McSwiggen et al.
9	5 624,803	04/29/97	Noonberg et al.
10	5 625,047	04/29/97	Been et al.
11	5 627,053	05/06/97	Usman, et al.
12	5 631,359	05/20/97	Chowriya et al.
13	5 633,133	05/27/97	Long et al.
14	5 672,695	09/30/97	Eckstein et al.
15	5 716,824	02/10/98	Beigelman, et al.
16	5 760,062	06/02/98	Gaeta et al.
17	5 767,278	06/16/98	Gaeta et al.
18	5 770,613	06/23/98	Gaeta et al.

Foreign Patent Documents

	Document Number	Date	Country
19	EP 0 360 257	09/20/89	EP (Hampel et al.)
20	WO 91 03162	03/21/91	WO (Rossi et al.)
21	WO 92 07065	04/30/92	WO (Eckstein et al.)
22	WO 93 15187	05/05/93	WO (Usman et al.)
23	WO 93/23057	11/25/93	WO (Thompson, et al.)
24	WO 93 23569	11/25/93	WO (Draper et al.)
25	WO 94 02595	02/03/94	WO (Sullivan et al.)
26	WO 95 04818	02/16/95	WO (Draper et al.)
27	WO 95 11304	04/27/95	WO (Usman et al.)
28	WO 95 13380	05/18/95	WO (Draper et al.)
29	WO 95 23225	08/31/95	WO (Stinchcomb et al.)
30	WO 96 10390	04/11/96	WO (Ansell, et al.)
31	WO 96 10391	04/11/96	WO (Choi et al.)
32	WO 96 10392	04/11/96	WO (Holland et al.)
33	WO 96 18736	06/20/96	WO (Beigelman)
34	WO 96 19577	06/27/96	WO (Collins)
35	WO 96 22689	08/01/96	WO (Pyle et al.)
36	WO 97 26270	07/24/97	WO (Wincott et al.)
37	WO 98 01542	01/15/98	WO (Collins et al.)
38	WO 98 13526	04/02/98	WO (Woolf et al.)
39	WO 98 14592	04/09/98	WO (Cech et al.)
40	WO 98 14593	04/09/98	WO (Cech et al.)
41	WO 98 28317	07/02/98	WO (Karpiesky et al.)
42	WO 98 43993	10/08/98	WO (Breaker et al.)
43	WO 98 58058	12/23/98	WO (Ludwig et al.)
44	WO 99 16871	04/08/99	WO (Eckstein et al.)
45	WO 99 55857	11/04/99	WO (Beigelman et al.)

Other Documents (Including Author, Title, Date, Pertinent Pages, Etc).

46 Abramovitz et al., "Catalytic Role of 2'-Hydroxyl Groups Within a Group II Intron Active Site," Science 271:1410-1413 (1996)

47 Akhtar and Juliano, "Cellular Uptake and Intracellular Fate of AntiSense Oligonucleotides," Trends Cell Biol. 2:139-144 (1992)

48 Banerjee and Turner, "The Time Dependence of Chemical Modification Reveals Slow Steps in the Folding of a Group I Ribozyme," Biochemistry 34:6504-6512 (1995)

49 Beaudry and Joyce, "Directed Evolution of an RNA Enzyme," Science 257:635-641 (1992)

50 Beigelman et al., "Chemical Modification of Hammerhead Ribozymes," J. Biol. Chem. 270:25702-25708 (1995)

51 Bellon et al., "Amino-Linked Ribozymes: Post-Synthetic Conjugation of Half-Ribozymes," Nucleosides & Nucleotides 16:951-954 (1997)

52 Berzal-Herranz et al., "Essential nucleotide sequences and secondary structure elements of the hairpin ribozyme," EMBO J. 12:2567-2574 (1993)

53 Berzal-Herranz et al., "In vitro selection of active hairpin ribozymes by sequential RNA-catalyzed cleavage and ligation reactions," Genes & Development 6:129-134 (1992)

54 Bevilacqua et al., "A Mechanistic Framework for the Second Step of Splicing Catalyzed by the *Tetrahymena* Ribozyme," Biochemistry 35:648-658 (1996)

55 Blackburn, "E., 1990, JBC, 265, 5919-5921

56 Breaker and Joyce, "Inventing and improving ribozyme function: rational design versus iterative selection
methods," TIBTECH 12:268-275 (1994)

57 Breaker et al., "A DNA enzyme with Mg²⁺-dependent RNA phosphoesterase activity," Chemistry & Biology
2(10):655-660 (1995)

58 Breaker, "Are engineered proteins getting competition from RNA?" Current Opinion in Biotechnology 7:442-
448 (1996)

59 Burgin et al., "Chemically Modified Hammerhead Ribozymes with Improved Catalytic Rates," Biochemistry
35:14090-14097 (1996) (volume no mistakenly listed as 6)

60 Burke et al., "Structural Analysis and Modifications of the Hairpin Ribozyme," Nucleic Acids and Molecular
Biology, edited by Eckstein and Lilley, Springer-Verlag Berlin Heidelberg, 10:129-143 (1996)

61 Caruthers et al., "Chemical Synthesis of Deoxyoligonucleotides and Deoxyoligonucleotide Analogs," Methods
in Enzymology 211:3-19 (1992)

62 Cech et al., "Representation of the secondary and tertiary structure of group I introns," nature structural
biology 1:273-280 (1994)

63 Cech, "Ribozymes and Their Medical Implications," JAMA 260:3030-3034 (1988)

64 Chartrand et al., "An oligodeoxyribonucleotide that supports catalytic activity in the hammerhead ribozyme
domain," Nucleic Acids Research 23(20):4092-4096 (1995)

65 Chen et al., "Multitarget-Ribozyme Directed to Cleave at up to Nine Highly Conserved HIV-1 env RNA
Regions Inhibits HIV-1 Replication-Potential Effectiveness Against Most Presently Sequenced HIV-1 Isolates,"
Nucleic Acids Research 20:4581-4589 (1992)

66 Chowrira et al., "In Vitro and in Vivo Comparison of Hammerhead, Hairpin, and Hepatitis Delta Virus Self-
Processing Ribozyme Cassettes," J. Biol. Chem. 269:25856-25864 (1994)

67 Chowrira et al., "Novel guanosine requirement for catalysis by the hairpin ribozyme," Nature 354:320-322
(1991)

68 Christoffersen and Marr, "Ribozymes as Human Therapeutic Agents," J. Med. Chem. 38:2023-2037 (1995)
(also referred to as Christofferson and Marr)

69 Christofferson et al., "Application of computational technologies to ribozyme biotechnology products," Journal
of Molecular Structure (Theochem) 311:273-284 (1994) (Christoffersen)

70 Collins and Olive, "Reaction Conditions and Kinetics of Self-Cleavage of a Ribozyme Derived From
Neurospora VS RNA," Biochemistry 32:2795-2799 (1993)

71 Couture and Stinchcomb, "Anti-gene therapy: the use of ribozymes to inhibit gene function," Trends In
Genetics 12:510-515 (1996)

72 Daniels et al., "Two Competing Pathways for Self-splicing by Group II Introns: A Quantitative Analysis of *in
Vitro* Reaction Rates and Products," J. Mol. Biol. 256:31-49 (1996)

73 Dreyfus, "Restriction Ribozymes?" Einstein Quarterly Journal of Biology and Medicine 6:92-93 (1988)

74 Duval-Valentin, "Specific inhibition of transcription by triple helix-forming oligonucleotides," Proc. Natl. Acad.
Sci. USA 89 504-508 (1992)

75 Egholm et al., "PNA hybridizes to complementary oligonucleotides obeying the Watson-Crick hydrogen-
bonding rules," Nature 365:566-568 (1993)

76 Elroy-Stein and Moss, "Cytoplasmic Expression System Based on Constitutive Synthesis of Bacteriophage T7
RNA Polymerase in Mammalian Cells," Proc. Natl. Acad. Sci. USA 87:6743-6747 (1990)

77 Feldstein et al., "Two sequences participating in the autolytic processing of satellite tobacco ringspot virus
complementary RNA," Gene 82:53-61 (1989)

78 Feng et al., "The RNA Component of Human Telomerase," Science 269:1236-1241 (1995)

79 Forster and Altman, "External Guide Sequences for an RNA Enzyme," Science 249:783-786 (1990)

80 Freier et al., "Improved free-energy parameters for predictions of RNA duplex stability," Proc. Natl. Acad. Sci.
USA 83:9373-9377 (1986)

81 Gao and Huang, "Cytoplasmic Expression of a Reporter Gene by Co-Delivery of T7 RNA Polymerase and T7
Promoter Sequence with Cationic Liposomes," Nucleic Acids Research 21:2867-2872 (1993)

82 Good et al., "Expression of small, therapeutic RNAs in human nuclei," Gene Therapy 4:45-54 (1997)

83 Grasby et al., "Purine Functional Groups in Essential Residues of the Hairpin Ribozyme Required for Catalytic
Cleavage of RNA," Biochemistry 34:4068-4076 (1995)

84 Griffin et al., "Group II intron ribozymes that cleave DNA and RNA linkages with similar efficiency, and lack
contacts with substrate 2'-hydroxyl groups," Chemistry & Biology 2:761-770 (1995)

85 Guerrier-Takada et al., "The RNA Moiety of Ribonuclease P Is the Catalytic Subunit of the Enzyme," Cell 35:849-857 (1983)

86 Guo and Collins, "Efficient *trans*-cleavage of a stem-loop RNA substrate by a ribozyme derived from *Neurospora* VS RNA," EMBO J. 14:368-376 (1995)

87 Hampel and Tritz, "RNA Catalytic Properties of the Minimum (-)sTRSV Sequence," Biochemistry 28:4929-4933 (1989)

88 Hampel et al., "Hairpin' Catalytic RNA Model: Evidence for Helices and Sequence Requirement for Substrate RNA," Nucleic Acids Research 18:299-304 (1990)

89 Harris et al., "Identification of phosphates involved in catalysis by the ribozyme RNase P RNA," RNA 1:210-218 (1995)

90 Haseloff and Gerlach, "Sequences required for self-catalysed cleavage of the satellite RNA of tobacco ringspot virus," Gene 82:43-52 (1989)

91 Haseloff and Gerlach, "Simple RNA Enzymes with New and Highly Specific Endoribonuclease Activities," Nature 334:585-591 (1988)

92 Hegg et al., "Kinetics and Thermodynamics of Intermolecular Catalysis by Hairpin Ribozymes," Biochemistry 34:15813-15828 (1995)

93 Herschlag and Cech, "Catalysis of RNA Cleavage by the *Tetrahymena thermophila* Ribozyme 1. Kinetic Description of the Reaction of an RNA Substrate Complementary to the Active Site," Biochemistry 29:10159-10171 (1990)

94 Hertel et al., "A Kinetic Thermodynamic Framework for the Hammerhead Ribozyme Reaction," Biochemistry 33:3374-3385 (1994)

95 Hertel et al., "Numbering System for the Hammerhead," Nucleic Acids Research 20:3252 (1992)

96 Ishiwata et al., "Physical-Chemistry Characteristics and Biodistribution of Poly(ethylene glycol)-Coated Liposomes Using Poly(oxyethylene) Cholesteryl Ether," Chem. Pharm. Bull. 43:1005-1011 (1995) (mistakenly referred to as Ishiwataet)

97 Izant and Weintraub, "Constitutive and Conditional Suppression of Exogenous and Endogeneous Genes by Anti-Sense RNA," Science 229:345-352 (1985)

98 Jaeger et al., "Improved Predictions of Secondary Structures for RNA," Proc. Natl. Acad. Sci. USA 86:7706-7710 (1989)

99 Jeffries and Symons, "A Catalytic 13-mer Ribozyme," Nucleic Acids Research 17:1371-1377 (1989) (also referred to as Jefferies)

100 Joseph et al., "Substrate selection rules for the hairpin ribozyme determined by in vitro selection, mutation, and analysis of mismatched substrates," Genes & Development 7:130-138 (1993)

101 Joyce et al., "Amplification, mutation and selection of catalytic RNA," Gene 82:83-87 (1989)

102 Joyce, "Directed Molecular Evolution," Scientific American 267:90-97 (1992)

103 Karpeisky et al., "Highly Efficient Synthesis of 2'-O-Amino Nucleosides And Their Incorporation in Hammerhead Ribozymes," Tetrahedron Letters 39:1131-1134 (1998)

104 Kashani-Sabet et al., "Reversal of the Malignant Phenotype by an Anti-ras Ribozyme," Antisense Research & Development 2:3-15 (1992)

105 Kim and Cech, "Three-dimensional model of the active site of the self-splicing rRNA precursor of *Tetrahymena*," Proc. Natl. Acad. Sci. USA 84:8788-8792 (1987)

106 Kim et al., "Specific Association of Human Telomerase Activity with Immortal Cells and Cancer," Science 266:2011-2015 (1994)

107 Knitt et al., "pH Dependencies of the *Tetrahymena* Ribozyme Reveal an Unconventional Origin of an Apparent pK_a," Biochemistry 35:1560-1570 (1996)

108 Kore, et al., "Sequence specificity of the hammerhead ribozyme revisited; the NIH rule", Nucleic Acids Research, 26(18):4116-4120 (1998).

109 Kumar and Ellington, "Artificial evolution and natural ribozymes," FASEB J. 9:1183-1195 (1995)

110 Lasic and Needham "The 'Stealth' Liposome: A Prototypical Biomaterial," Chemical Reviews 95:2601-2627 (1995)

111 Lasic and Papahadjopoulos, "Liposomes Revisited," Science 267:1275-1276 (1995)

112 L'Huillier et al., "Cytoplasmic Delivery of Ribozymes Leads to Efficient Reduction in α -Lactalbumin mRNA Levels in C1271 Mouse," EMBO J. 11:4411-4418 (1992)

113 Li and Altman, "Cleavage by RNase P of gene N mRNA reduces bacteriophage λ burst size," Nucleic Acids Research 24:835-842 (1996)

114 Li et al., "Thermodynamic and Activation Parameters for Binding of a Pyrene-Labeled Substrate by the *Tetrahymena* Ribozyme: Docking is Not Diffusion-Controlled and is Driven by a Favorable Entropy Change," *Biochemistry* 34:14394-14399 (1995)

115 Lieber et al., "Stable High-Level Gene Expression in Mammalian Cells by T7 Phage RNA Polymerase," *Methods Enzymol.* 217:47-66 (1993)

116 Limbach et al., "Summary: the modified nucleosides of RNA," *Nucleic Acids Research* 22(12):2183-2196 (1994)

117 Lisacek et al., "Automatic Identification of Group I Intron Cores in Genomic DNA Sequences," *J. Mol. Biol.* 235:1206-1217 (1994)

118 Lisziewicz et al., "Inhibition of Human Immunodeficiency Virus Type 1 Replication by Regulated Expression of a Polymeric Tat Activation Response RNA Decoy as a Strategy for Gene Therapy in AIDS," *Proc. Natl. Acad. Sci. U.S.A.* 90:8000-8004 (1993)

119 Liu et al., "Cationic Liposome-mediated Intravenous Gene Delivery," *J. Biol. Chem.* 270(42):24864-24870 (1995)

120 McGarry and Lindquist, "Inhibition of heat shock protein synthesis by heat-inducible antisense RNA," *Proc. Natl. Acad. Sci. USA* 83:399-403 (1986)

121 McKay, "Structure and function of the hammerhead ribozyme: an unfinished story," *RNA* 2:395-403 (1996)

122 Michel and Westhof, "Slippery substrates," *Nat. Struct. Biol.* 1:5-7 (1994)

123 Michel et al., "Structure and Activities of Group II Introns," *Annu. Rev. Biochem.* 64:435-461 (1995)

124 Michels and Pyle, "Conversion of a Group II Intron into a New Multiple-Turnover Ribozyme that Selectively Cleaves Oligonucleotides: Elucidation of Reaction Mechanism and Structure/Function Relationships," *Biochemistry* 34:2965-2977 (1995)

125 Milligan and Uhlenbeck, "Synthesis of Small RNAs Using T7 RNA Polymerase," *Methods Enzymol.* 180:51-62 (1989)

126 Mitra et al., "A mammalian 2'-5'A system functions as an antiviral pathway in transgenic plants," *Proc. Natl. Acad. Sci. USA* 93:6780-6785 (1996)

127 Mohr et al., "A tyrosyl-tRNA synthetase can function similarly to an RNA structure in the *Tetrahymena* ribozyme," *Nature* 370:147-150 (1994)

128 Moore and Sharp, "Site-Specific Modification of Pre-mRNA: The 2'-Hydroxyl Groups at the Splice Sites," *Science* 256:992-996 (1992)

129 Mukhopadhyay et al., "Antisense Regulation of Oncogenes in Human Cancer," *Critical Reviews in Oncogenesis* 7:151-190 (1996)

130 Nathans and Smith, "Restriction Endonucleases in the Analysis and Restructuring of DNA Molecules," *Ann. Rev. Biochem.* 44:273-293 (1975)

131 Ohkawa et al., "Activities of HIV-RNA Targeted Ribozymes Transcribed From a 'Shot-Gun' Type Ribozyme-trimming Plasmid," *Nucleic Acids Symp. Ser.* 27:15-16 (1992)

132 Ojwang et al., "Inhibition of Human Immunodeficiency Virus Type 1 Expression by a Hairpin Ribozyme," *Proc. Natl. Acad. Sci. USA* 89:10802-10806 (1992)

133 Oku et al., "Real-time analysis of liposomal trafficking in tumor-bearing mice by use of positron emission tomography," *Biochimica et Biophysica Acta* 1238:86-90 (1995)

134 Orgel, "Selection *in vitro*," *Proc. R. Soc. London B.* 205:435-442 (1979)

135 Pace and Smith, "Ribonuclease P: Function and Variation," *J. Biol. Chem.* 265:3587-3590 (1990)

136 Pan et al., "Probing of tertiary interactions in RNA: 2'-Hydroxyl-base contacts between the Rnase P and pre-tRNA," *Proc. Natl. Acad. Sci. USA* 92:12510-12514 (1995)

137 Perreault et al., "Mixed Deoxyribo- and Ribo-Oligonucleotides with Catalytic Activity," *Nature* 344:565-567 (1990) (often mistakenly listed as Perrault)

138 Perrotta and Been, "A pseudoknot-like structure required for efficient self-cleavage of hepatitis delta virus RNA," *Nature* 350:434-436 (1991)

139 Perrotta and Been, "Cleavage of Oligoribonucleotides by a Ribozyme Derived from the Hepatitis D Virus RNA Sequence," *Biochemistry* 31:16-21 (1992)

140 Pieken et al., "Kinetic Characterization of Ribonuclease-Resistant 2'-Modified Hammerhead Ribozymes," *Science* 253:314-317 (1991)

141 Puttaraju et al., "A circular trans-acting hepatitis delta virus ribozyme," *Nucleic Acids Research* 21:4253-4258 (1993)

142 Pyle et al., "Building a Kinetic Framework for Group II Intron Ribozyme Activity: Quantitation of Interdomain Binding and Reaction Rate," *Biochemistry* 33:2716-2725 (1994)

143 Robertson et al., "Purification and Properties of a Specific *Escherichia coli* Ribonuclease which Cleaves a Tyrosine Transfer Ribonucleic Acid Precursor," J. Biol. Chem. 247:5243-5251 (1972)

144 Rossi et al., "Ribozymes as Anti-HIV-1 Therapeutic Agents: Principles, Applications, and Problems," Aids Research and Human Retroviruses 8:183-189 (1992)

145 Santoro and Joyce, "A general purpose RNA-cleaving DNA enzyme," Proc. Natl. Acad. Sci. USA 94:4262-4266 (1997)

146 Sarver et al., "Ribozymes as Potential Anti-HIV-1 Therapeutic Agents" Science 247:1222-1225 (1990)

147 Saville and Collins, "A Site-Specific Self-Cleavage Reaction Performed by a Novel RNA In Neurospora Mitochondria," Cell 61:685-696 (1990)

148 Saville and Collins, "RNA-Mediated Ligation of Self-Cleavage Products of a *Neurospora* Mitochondrial Plasmid Transcript," Proc. Natl. Acad. Sci. USA 88:8826-8830 (1991)

149 Scanlon et al., "Ribozyme-Mediated Cleavage of c-fos mRNA Reduces Gene Expression of DNA Synthesis Enzymes and Metallothionein," Proc. Natl. Acad. Sci. USA 88:10591-10595 (1991)

150 Scaringe et al., "Chemical synthesis of biologically active oligoribonucleotides using β -cyanoethyl protected ribonucleoside phosphoramidites," Nucl. Acids Res. 18:5433-5441 (1990)

151 Schmidt et al., "Base and sugar requirements for RNA cleavage of essential nucleoside residues in internal loop B of the hairpin ribozyme: implications for secondary structure," Nucleic Acids Research 24:573-581 (1996)

152 Scott et al., "The crystal structure of an All-RNA hammerhead ribozyme: A proposed mechanism for RNA catalytic cleavage," Cell 81:991-1002 (1995)

153 Shabarova et al., "Chemical ligation of DNA: The first non-enzymatic assembly of a biologically active gene," Nucleic Acids Research 19:4247-4251 (1991)

154 Stein and Cheng, "Antisense Oligonucleotides as Therapeutic Agents - Is the Bullet Really Magical?" Science 261:1004-1288 (1993)

155 Strobel et al., "Exocyclic Amine of the Conserved G-U Pair at the Cleavage Site of the *Tetrahymena* Ribozyme Contributes to 5'-Splice Site Selection and Transition State Stabilization," Biochemistry 35:1201-1211 (1996)

156 Strobel et al., "Minor Groove Recognition of the Conserved G-U Pair at the *Tetrahymena* Ribozyme Reaction Site," Science 267:675-679 (1995)

157 Sullenger and Cech, "Ribozyme-mediated repair of defective mRNA by targeted trans-splicing," Nature 371:619-622 (1994)

158 Sullenger and Cech, "Tethering Ribozymes to a Retroviral Packaging Signal for Destruction of Viral RNA," Science 262:1566-1569 (1993)

159 Szostak, "In Vitro Genetics," TIBS 17:89-93 (1993)

160 Taira et al., "Construction of a novel RNA-transcript-trimming plasmid which can be used both *in vitro* in place of run-off and (G)-free transcriptions and *in vivo* as multi-sequences transcription vectors," Nucleic Acids Research 19:5125-5130 (1991)

161 Tang and Breaker, "Examination of the catalytic fitness of the hammerhead ribozyme by *in vitro* selection," RNA 3:914-925 (1997)

162 Thompson et al., "Improved accumulation and activity of ribozymes expressed from a tRNA-based RNA polymerase III promoter," Nucleic Acids Research 23:2259-2268 (1995)

163 Torrence et al., "Targeting RNA for degradation with a (2'-5') oligoadenylate-antisense chimera," Proc. Natl. Acad. Sci. USA 90:1300-1304 (1993)

164 Turner et al., "Improved Parameters for Prediction of RNA Structure," Cold Spring Harbor Symposia on Quantitative Biology Volume LII, pp. 123-133 (1987)

165 Turner et al., "Free Energy Increments for Hydrogen Bonds in Nucleic Acid Base Pairs," J. Am. Chem. Soc. 109:3783-3785 (1987)

166 Uhlenbeck, "A Small Catalytic Oligoribonucleotide," Nature 328:596-600 (1987) (this is listed as Nature 327 in the various specifications, but it is actually 328)

167 Usman and Cedergren, "Exploiting the chemical synthesis of RNA," TIBS 17:334-339 (1992)

168 Usman and McSwiggen, "Ch. 30 - Catalytic RNA (Ribozymes) as Drugs," Annual Reports in Medicinal Chemistry 30:285-294 (1995)

169 Usman et al., "Automated Chemical Synthesis of Long Oligoribonucleotides Using 2'-O-Silylated Ribonucleoside 3'-O-Phosphoramidites on a Controlled-Pore Glass Support: Synthesis of a 43-Nucleotide Sequence Similar to the 3'-Half Molecule of an *Escherichia coli* Formylmethionine tRNA," J. Am. Chem. Soc. 109:7845-7854 (1987)

170 Usman et al., "Chemical modification of hammerhead ribozymes: activity and nuclease resistance," Nucleic Acids Symposium Series 31:163-164 (1994)

171 Usman et al., "Hammerhead ribozyme engineering," Current Opinion in Structural Biology 1:527-533(1996)

172 Vaish et al., "Isolation of Hammerhead Ribozymes with Altered Core Sequences by *in Vitro* Selection," Biochemistry 36:6495-6501 (1997)

173 Ventura et al., "Activation of HIV-Specific Ribozyme Activity by Self-Cleavage," Nucleic Acids Research 21:3249-3255 (1993)

175 Weerasinghe et al., "Resistance to Human Immunodeficiency Virus Type 1 (HIV-1) Infection in Human CD4⁺ Lymphocyte-Derived Cell Lines Conferred by Using Retroviral Vectors Expressing an HIV-1 RNA-Specific Ribozyme," Journal of Virology 65:5531-5534 (1994)

176 Wincott et al., "Synthesis, deprotection, analysis and purification of RNA and ribozymes," Nucleic Acids Research 23(14):2677-2684 (1995)

177 Wincott et al., "A Practical Method for the Production of RNA and Ribozymes," Methods in Molecular Biology 74:59-69 (1997)

178 Wu-Pong, "Oligonucleotides: Opportunities for Drug Therapy and Research," BioPharm pp20-33 (1994)

179 Yu et al., "A Hairpin Ribozyme Inhibits Expression of Diverse Strains of Human Immunodeficiency Virus Type 1," Proc. Natl. Acad. Sci. USA 90:6340-6344 (1993)

180 Yuan et al., "Targeted cleavage of mRNA by human RNase P," Proc. Natl. Acad. Sci. USA 89:8006-8010 (1992)

182 Zarrinkar and Williamson, "The P9.1-P9.2 peripheral extension helps guide folding of the *Tetrahymena* ribozyme," Nucleic Acids Research 24:854-858 (1996)

183 Zaug et al., "The *Tetrahymena* Ribozyme Acts Like an RNA Restriction Endonuclease," Nature 324:429-433 (1986)

184 Zhou et al., "Synthesis of Functional mRNA in Mammalian Cells by Bacteriophage T3 RNA Polymerase," Mol. Cell. Biol. 10:4529-4537 (1990)

185 Zimmerly et al., "A Group II Intron RNA is a Catalytic Component of a DNA Endonuclease Involved in Intron Mobility," Cell 83:529-538 (1995)

In accordance with MPEP Sections 609 and 707.05(b), it is requested the document cited (including any cited in applicant's specification which is not repeated on the attached Form PTO-1449) be given thorough consideration and that it be cited of record in the prosecution history of the present application by initialing on Form PTO-1449. Such initialing is requested even if the Examiner does not consider a cited document to be sufficiently pertinent to use in a rejection, or otherwise does not consider it to be prior art for any reason, or even if the Examiner does not

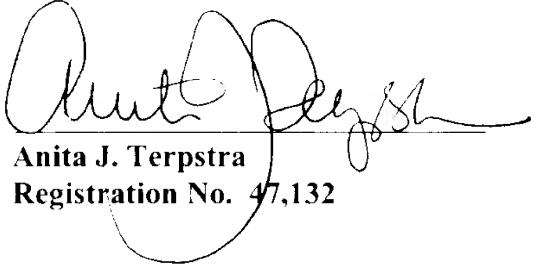
believe that the guidelines for citation have been fully complied with. This is requested so that each document becomes listed on the face of the patent issuing on the present application.

Respectfully submitted,

McDonnell Boehnen Hulbert & Berghoff

Date: 11/02/1998

By:


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